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Associations between circulating components of the renin-angiotensin-aldosterone system and left ventricular mass

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Abstract

***Objective*—Cardiac growth may be modulated in part by the trophic effects of neurohormones. The aim of the present study was to investigate the relation between the basal activity of the renin-angiotensin-aldosterone system and left ventricular mass.**

***Design*—A population based sample of 615 middle-aged subjects was studied by standardised echocardiography; anthropometric measurements; and biochemical quantification of renin, pro-renin, angiotensinogen, angiotensin converting enzyme (ACE), and aldosterone.**

***Results*—Echocardiographic left ventricular mass index correlated significantly with arterial blood pressure, age, and body mass index. In addition, in men ACE activity was significantly related to left ventricular mass index in univariate (P = 0·0007) and multivariate analyses (P = 0·008). Men with left ventricular hypertrophy presented with significantly higher serum ACE concentrations than those with normal left ventricular mass index (P = 0·002). In both men and women serum aldosterone was strongly related to septal and posterior wall thickness. Furthermore, in women serum aldosterone was positively and independently associated with left ventricular mass index (P = 0·0001). This effect was most prominent in hypertensive women. Finally, women with left ventricular hypertrophy presented with significantly higher serum aldosterone (P = 0·01). No significant associations with left ventricular mass index were observed for angiotensinogen, renin, or pro-renin.**

***Conclusions*—The data suggest that the variability of serum ACE or aldosterone, as occurred in this large population based sample, may contribute to the modulation of left ventricular mass.**

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Keywords: angiotensin converting enzyme; aldosterone; angiotensinogen; left ventricular hypertrophy

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Left ventricular hypertrophy is associated with a markedly increased incidence of myocardial infarction,[1] heart failure, or premature death.[2–4] Traditionally, chronic pressure overload of the heart, imposed by arterial hypertension or valvar heart disease, is considered to be the aetiological factor responsible for this major risk factor.[5] In recent years, however, experimental investigations directed interest to the question whether neurohormonal stimulation may contribute to the development of left ventricular hypertrophy.[6] In particular, numerous studies on isolated myocytes or isolated experimental hearts provided convincing evidence that angiotensin II or adrenergic agonists may accelerate myocardial growth even when haemodynamic load is low.[7–9]

Further attention was drawn to these results by the demonstration that a deletion polymorphism of the angiotensin converting enzyme (ACE) gene may be associated with left ventricular hypertrophy as determined by electrocardiography[10] or echocardiography.[11 12] Genetically determined chronic increases in circulating or tissue concentrations of ACE activity found in subjects carrying the deletion allele[13 14] offer a potential mechanism to account for the increased risk of left ventricular hypertrophy. However, a recent report failed to demonstrate any association between the ACE deletion polymorphism and echocardiographic left ventricular mass.[15] The ACE deletion polymorphism, however, represents only about 20% of the interindividual variability of plasma and tissue ACE activities.[16–18]

In addition to the rather modest effect of the ACE deletion polymorphism on ACE protein concentrations, genetic variants employed in linkage or association studies by definition represent a genomic locus rather than a specific gene. Therefore, the major aim of the present investigation was to address the question whether, in a population based sample, ACE activity in and of itself was related to left ventricular mass. Furthermore, the relations of left ventricular mass to renin, pro-renin, angiotensinogen, and aldosterone concentrations were systematically investigated.

Subjects and methods

STUDY POPULATION

The subjects of this study had initially participated in the MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease), Augsburg, baseline survey of 1984/85 and its follow up examination in 1987/88.[19] Subjects originate from a sex-age-stratified random sample of all German residents of the Augsburg study area. In 1994, a second follow up examination including electrocardiographic, echocardiographic, biochemical, and anthropometric measurements was offered to a total of 1010

men and women, aged 52 to 65 years, of whom 615 (61%) attended.

All subjects responded to a questionnaire on medical history, physical activities, medication, and personal habits. Body height and weight were recorded in light clothing, and body mass index was computed as weight in kg divided by height in metre squared (kg/m^2). Resting blood pressures was measured after subjects had been sitting for at least 30 minutes. A mercury sphygmomanometer was used to measure blood pressure three times at the right arm by two investigators. The mean of three measurements was used for this study. Hypertension was defined as systolic blood pressure $\geqslant$ 160 mm Hg, or diastolic blood pressure $\geqslant$ 95 mm Hg or when subjects were taking long term antihypertensive medication, borderline hypertension was defined as a blood pressure equal or above 140/90 mm Hg and below 160/95 mm Hg, and normotension was defined as blood pressure values below 140/90 mm Hg. Subjects with valvar heart disease (n = 2) and those taking ACE inhibitors (n = 24) were excluded from further analysis.

ECHOCARDIOGRAPHIC MEASUREMENTS

A two dimensionally guided M mode echocardiogram was performed on each subject by one of two expert sonographers (Sonos 1500, Hewlett Packard). M mode tracings were recorded on stripchart paper at 50 mm/s. Only tracings that demonstrated optimal visualisation of left ventricular interfaces were used, a requirement that resulted in exclusion of 17% of potential subjects. To reduce interobserver variability,[20] all M mode tracings were analysed by one cardiologist. The cardiologist was blinded to the clinical and biochemical data. Measurements for M mode guided calculation of left ventricular mass were taken just below the tip of the mitral valve. Left ventricular internal end diastolic (EDD) and end systolic dimensions (ESD) and septal (SWth) and posterior wall thickness (PWth) were measured according to the guidelines of the American Society of Echocardiography.[21] Left ventricular mass (LVM) was calculated from M mode echocardiograms according to the formula described by Devereux *et al*[22]:

Left ventricular mass M mode (g) = $0{\cdot}8\ (1{\cdot}04\ [EDD + SWth + PWth]^3 - EDD^3) + 0{\cdot}6g$

Left ventricular mass was indexed to body surface area as left ventricular mass index in g/m^2 body surface area. Left ventricular hypertrophy by M mode criteria was considered when left ventricular mass index > 134 g/m^2 body surface area in men or > 110 g/m^2 body surface area in women.[22] Patterns of left ventricular geometry were defined as previously proposed by Ganau *et al*—that is, normal geometry when left ventricular mass index was normal and relative wall thickness ($2 \times PWth/EDD$) < 0·45, left ventricular remodelling when normal left ventricular mass index was combined with relative wall thickness > 0·45, concentric left ventricular hypertrophy when left ventricular hypertrophy occurred with a relative wall thickness > 0·45, and eccentric left ventricular hypertrophy when left ventricular hypertrophy and a relative wall thickness < 0·45 were combined.[23]

BIOCHEMICAL MEASUREMENTS

Blood was drawn from non-fasting subjects who were in a supine resting position for at least 30 minutes. All determinations of circulating components of the renin-angiotensin system were carried out in duplicate. Immunoreactive renin was measured in a 200 μl plasma sample by means of an immunoradiometric assay kit (Nichols Institute, Wychen, The Netherlands), following the methods proposed by Derkx *et al*.[24 25] The concentration of pro-renin was calculated by subtracting the results obtained before activation of pro-renin (that is active renin) from those obtained after activation (that is total renin). Pro-renin was activated non-proteolytically, using the renin inhibitor remikiren. Aldosterone was quantified in 100 μl serum by standard radioimmunoassay (Peninsula, Belmont, CA). For determination of angiotensinogen in 10 μl serum, 50 ng recombinant human renin (a generous gift of Dr Fischli, Hoffmann-LaRoche, Basel, Switzerland) was used to generate angiotensin I as previously described.[26] Angiotensin I was measured by standard radioimmunoassay (Peninsula, Belmont, CA). Angiotensin converting enzyme activity was determined by a fluorometric assay as described in detail elsewhere.[27]

STATISTICAL ANALYSIS

Values measured for serum aldosterone, angiotensinogen, renin, and pro-renin were not normally distributed and were skewed to the right. Therefore, the correlation and regression analyses were performed on logarithmically transformed values to take account of the deviation from normal distribution. However, the use of non-transformed values confirmed the principal observations with respect to these components of the renin angiotensin system. ACE activity was almost normally distributed in our study sample and the use of logarithmically transformed values did not result in perceivable differences in results. Therefore, all analyses that include ACE activity are presented as an untransformed variable.

To assess the statistical significance of differences in mean values between subjects with normal and raised left ventricular mass indices we used *t* tests to compare independent samples. Univariate linear associations between measures of left ventricular mass and circulating components of the renin-angiotensin system were assessed by calculation of Pearson's and Spearman's rank coefficients of correlation. After log-transformation of all skewed components of the renin-angiotensin-aldosterone system there were no marked quantitative differences between the two types of coefficients and here we report results for Pearson's correlation coefficient only. Multivariate analyses were run separately for men and women by computation of partial correlation coefficients. Each component of

Table 1 Anthropometric and biochemical data of participants according to the presence or absence of left ventricular hypertrophy (LVH) (mean) (SEM))

Variables	Men		Women	
	Normal LVMI (n = 179)	LVH (n = 32)	Normal LVMI (n = 227)	LVH (n = 48)
Age (y)	57·5 (0·3)	57·8 (0·8)	57·4 (0·2)	59·8 (0·7)†
BMI (kg/m²)	27·2 (0·2)	27·6 (0·6)	26·5 (0·03)	29·6 (0·9)†
Systolic BP (mm Hg)	145 (1)	153 (3)*	142 (1)	162 (2)†
Diastolic BP (mm Hg)	91 (0·2)	96 (2)*	87 (0·6)	97 (1·4)†
LVMI (g/m²)	95·3 (1·4)	158·6 (4·9)†	78·1 (1·0)	128·0 (1·5)†
Septal wall (mm)	10·8 (0·1)	15·1 (0·4)†	9·3 (0·1)	13·9 (0·3)†
Posterior wall (mm)	9·1 (0·1)	12·3 (0·3)†	7·8 (0·1)	11·0 (0·2)†
ACE (U/l)	24·7 (0·5)	29·4 (1·4)†	25·3 (0·4)	26·4 (1·1)
Aldosterone (pg/ml)	137 (7)	142 (14)	123 (5)	252 (61)‡
Angiotensinogen (µg/ml)	0·95 (0·02)	1·01 (0·05)	1·18 (0·04)	1·12 (0·07)
Renin (pg/ml)	19·5 (1·07)	16·4 (2·7)	14·4 (0·6)	13·4 (1·6)
Pro-renin (pg/ml)	266 (13·5)	270 (40·5)	179 (6·2)	167 (14·2)

LVMI, left ventricular mass index by M mode echocardiography (ASE formula); LVH, left ventricular hypertrophy (LVMI > 134 g/m² in men or > 110 g/m² in women; BMI, body mass index; BP, blood pressure; ACE, serum angiotensin converting enzyme activity.
*P < 0·05 *v* subjects with normal LVMI; †P < 0·01 *v* subjects with normal LVMI; ‡P < 0·05, a non-parametric test (Kruskal-Wallis) was used to calculate significance because aldosterone concentrations were not normally distributed.

the renin-angiotensin system was assessed after controlling for systolic blood pressure, body mass index, and age. Covariance-adjusted means of the left ventricular mass across quartiles of ACE and logarithmically transformed (ln) aldosterone concentrations were calculated, after controlling for systolic blood pressure, body mass index, and age, by linear regression techniques and assessed for linearity by modelling the median values of each quartile as a continuous variable. Likewise, adjusted mean values of ACE and ln aldosterone concentrations were calculated in groups of subjects with differing types of left ventricular geometry. Stratification of the analyses for the potentially modifying effects of age and hypertension produced no evidence for statistical interaction and is therefore not included in this report.

Results

BLOOD PRESSURE, BODY MASS INDEX, AND AGE

Anthropometric data on subjects with normal left ventricular mass index (M mode echocardiography) and those with left ventricular hypertrophy evaluated in the present investigation are shown in table 1. In both men and women, systolic or diastolic arterial blood pressures were significantly related to left ventricular mass index (table 2). Closest associations were detected for systolic blood pressure (table 2). Furthermore, the prevalence of left ventricular hypertrophy increased from 3·3% in normotensive individuals, to 9·6% in those with borderline hypertension, and to 23·2% in those with manifest hypertension. Likewise, body mass index and age were found to be related to echocardiographic left ventricular mass index (table 2). Since systolic blood pressure, body mass index, and age in women revealed close associations with left ventricular mass index by echocardiography these variables were included as control variables in subsequent multivariate analyses.

Table 2 Pearson correlation coefficients of left ventricular mass indices and clinical variables

	Men (n = 211)		Women (n = 277)	
	r	P	r	P
Age (y)	0·08	NS	0·29	0·0001
BMI (kg/m² BSA)	0·23	0·0007	0·32	0·0001
Systolic BP (mm Hg)	0·30	0·0001	0·41	0·0001
Diastolic BP (mm Hg)	0·27	0·0001	0·39	0·0001
ACE (u/l)	0·23	0·0007	0·05	NS
ln aldosterone (pg/ml)	0·09	NS	0·25	0·0001
ln angiotensinogen (µg/ml)	0·05	NS	−0·01	NS
ln renin (pg/ml)	−0·09	NS	−0·13	0·03
ln pro renin (pg/ml)	−0·04	NS	−0·05	NS

Left ventricular mass index (g/m² BSA) by M mode echocardiography (ASE formula); BMI, body mass index; BP, blood pressure; ACE, serum angiotensin converting enzyme activity.

ANGIOTENSIN CONVERTING ENZYME

In men both septal wall thickness and posterior wall thickness of the left ventricle were significantly associated with serum ACE activity (table 3). No significant associations were observed between end diastolic dimension and serum ACE (table 3). However, left ventricular mass index displayed significant associations with serum ACE activity (table 2). In men associations between ACE activity and echocardiographic left ventricular mass index remained significant when subjects were excluded who were taking any form of antihypertensive medication including diuretics or displayed evidence of myocardial infarction (n = 162: $r = 0·20$, P = 0·009). Likewise, ACE activity was significantly associated with left ventricular mass index when only non-hypertensive men were considered (n = 97, $r = 0·24$, P = 0·02). The significant association between ACE activity and left ventricular mass

Table 3 Pearson correlation coefficients of left ventricular wall thickness or end diastolic dimension and serum angiotensin converting enzyme activity or aldosterone

Variable	Men (n = 211)						Women (n = 277)					
	SWth		PWth		LVEDD		SWth		PWth		LVEDD	
	r	P	r	P	r	P	r	P	r	P	r	P
ACE (U/l)	0·14	0·04	0·20	0·004	0·004	NS	0·07	NS	0·06	NS	−0·09	NS
ln aldosterone (pg/ml)	0·17	0·02	0·16	0·02	−0·17	0·02	0·27	0·001	0·28	0·0001	−0·09	NS

SWth and PWth, septal and posterior wall thickness by M mode echocardiography, respectively; LVEDD, left ventricular end diastolic diameter; ACE, serum angiotensin converting enzyme activity.

Table 4 Partial correlation coefficients of left ventricular mass index, left ventricular wall thickness, or end diastolic dimension and serum angiotensin converting enzyme activity or aldosterone

	Men (n = 211)								*Women (n = 277)*							
	LVMI		*SWth*		*PWth*		*LVEDD*		*LVMI*		*SWth*		*PWth*		*LVEDD*	
Variable	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
ACE (U/l)	0·21	0·008	0·15	0·02	0·21	0·002	NS		NS		NS		NS		NS	
ln aldosterone (pg/ml)	NS		NS		NS		NS		0·19	0·002	0·22	0·0003	0·24	0·0001	NS	

LVMI, left ventricular mass index (g/m² BSA); SWth, septal wall thickness (mm); PWth, posterior wall thickness (mm); LVEDD, and left ventricular end diastolic diameter (mm) have been adjusted for systolic blood pressure, age, and body mass index. ACE, serum angiotensin converting enzyme activity.

index persisted in multivariate analyses that accounted for systolic blood pressure, body mass index, and age (table 4). Furthermore, after adjustment for co-variables, the data allowed us to calculate that an increase of 10 U/l in ACE activity was associated with an increase of left ventricular mass index of 8·6 g/m² (95% confidence interval 3·2 to 13·9, P = 0·0021). When men were divided in quartiles of ACE activity (< 20·5, 20·5–25·0, 25·1–29·0, > 29 U/l) the co-variable-adjusted mean of left ventricular mass index (M mode echo) increased progressively (test for linear trend P < 0·02) (fig 1A). Men with left ventricular hypertrophy by ASE criteria presented with significantly higher serum ACE activity (table 1, P = 0·002). The highest levels of ACE activity were found in those men with an eccentric pattern of left ventricular hypertrophy (fig 2A).

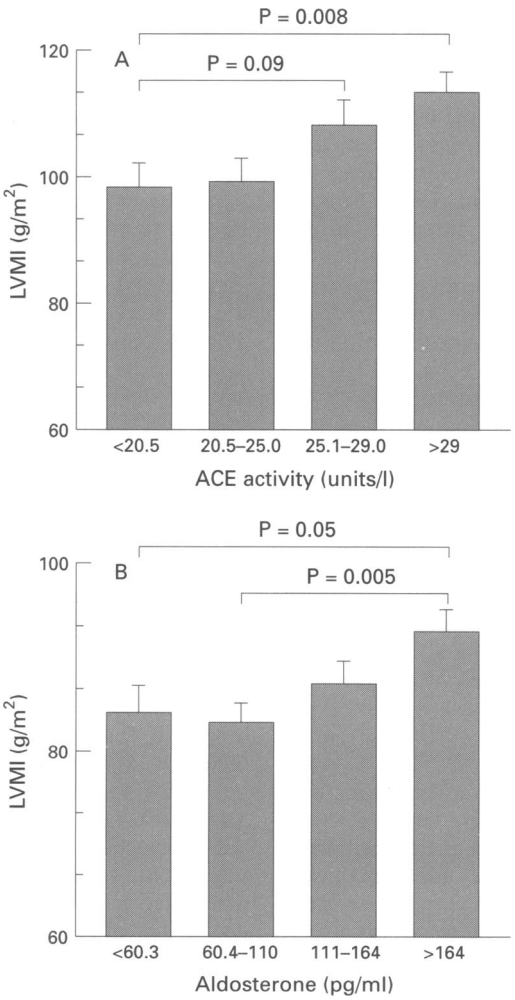

Figure 1 (A) Left ventricular mass index adjusted for systolic blood pressure, body mass index, and age in men according to serum ACE activity levels. Men were stratified by quartiles of serum ACE activity. LVMI represents left ventricular mass index. (B) Left ventricular mass index adjusted for systolic blood pressure, body mass index, and age in women according to serum aldosterone concentrations. Women were stratified by quartiles of serum aldosterone. LVMI, left ventricular mass index.

In women, no association between serum ACE activity and any of the indices of left ventricular mass was observed (tables 2 and 4).

ALDOSTERONE

In men univariate analysis showed significant associations between logarithmically transformed serum aldosterone concentration (ln

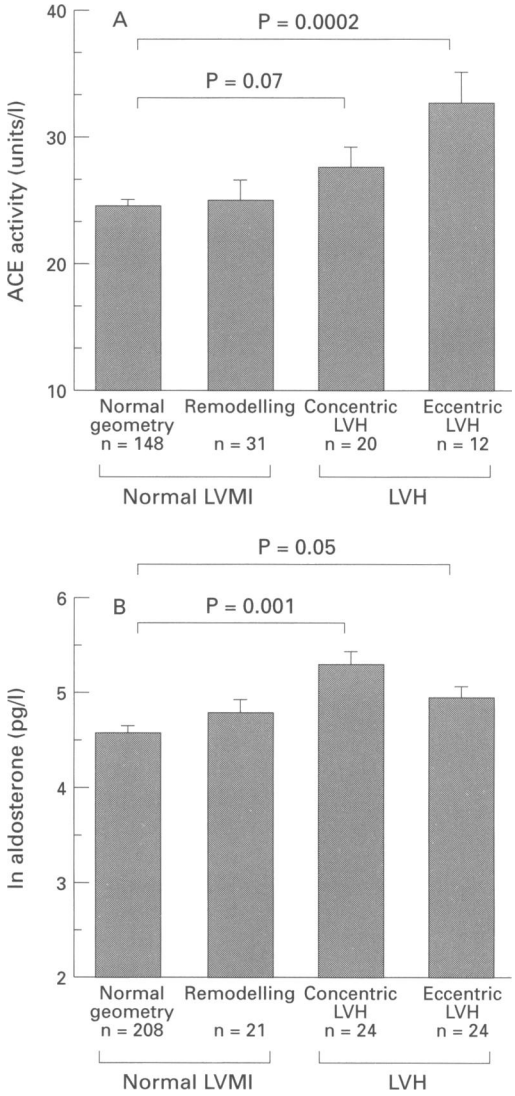

Figure 2 (A) Serum ACE activity in men according to left ventricular geometry. ACE acivity was highest in men with eccentric left ventricular hypertrophy. LVMI, left ventricular mass index; LVH, left ventricular hypertrophy. (B) Serum aldosterone concentrations in women according to left ventricular geometry. Concentrations of aldosterone were raised in women with concentric and eccentric left ventricular hypertrophy. Geometric patterns are defined in the methods section. LVMI, left ventricular mass index; LVH, left ventricular hypertrophy.

aldosterone) and both septal wall thickness and posterior wall thickness (table 3). Interestingly, there was a tendency towards smaller left ventricular end diastolic dimensions (table 3) that abolished significant associations with left ventricular mass index (table 2). Controlling for systolic blood pressure, body mass index, and age blunted the association of ln aldosterone with left ventricular wall thickness in men. However, a significant inverse correlation between ln aldosterone and end diastolic dimensions persisted ($\beta = -1{\cdot}51$, $P = 0{\cdot}006$). In men with left ventricular hypertrophy, ln aldosterone was not different from that in men with normal left ventricular mass (table 1).

In women significant univariate associations were observed between ln aldosterone and both septal or posterior wall thickness (table 3). In addition, significant associations were found between ln aldosterone and left ventricular mass index despite a slight but non-significant inverse association between ln aldosterone and end diastolic dimensions (tables 2 and 3). Significant correlations between ln aldosterone and left ventricular mass index were also found when we excluded women who were on any form of antihypertensive medication, including diuretics, or who displayed evidence of myocardial infarction (n = 219: $r = 0{\cdot}21$, $P = 0{\cdot}0015$). However, when only non-hypertensive women were considered, the association between ln aldosterone and left ventricular mass index was no longer detectable (n = 161, $r = 0{\cdot}07$, P = NS). Multivariate analyses that accounted for systolic blood pressure, body mass index, and age, confirmed a significant association between ln aldosterone and echocardiographic estimates of left ventricular mass index (table 4). After adjustment for covariables, the increase of aldosterone from 75 to 165 pg/l (equal to the interquartile difference in this sample) was associated with an increase of 4·1 g/m^2 in left ventricular mass index (95% confidence interval 1·7 to 7·3, $P = 0{\cdot}002$). When women were divided in quartiles of aldosterone concentration (< 60·3, 60·4–110, 111–164, > 164 pg/ml aldosterone; or < 4·1, 4·1–4·7, 4·8–5·0, > 5·1 ln aldosterone) the adjusted mean of left ventricular mass index increased progressively (test for linear trend ($P < 0{\cdot}03$) (fig 1B). Furthermore, aldosterone in women with left ventricular hypertrophy by ASE criteria was significantly higher than that in women with normal left ventricular mass ($P = 0{\cdot}0001$; table 1). Raised concentrations of ln aldosterone were found in women with concentric and eccentric patterns of left ventricular hypertrophy (fig 2B).

ANGIOTENSINOGEN

In both men and women no associations were observed between serum angiotensinogen concentration and any of indices of left ventricular mass (table 2). Furthermore, angiotensinogen concentrations in individuals with left ventricular hypertrophy by ASE criteria (table 1) did not differ significantly from those with normal left ventricular mass.

RENIN AND PRO-RENIN

No significant positive associations between left ventricular mass index and plasma renin or plasma pro-renin concentrations were detectable in either men or women (table 2). In fact, left ventricular mass index by M mode echocardiography in women was inversely associated with ln renin. However, significant inverse associations between systolic blood pressure and both ln renin and ln pro-renin concentrations ($r = -0{\cdot}14$; $P = 0{\cdot}05$; $r = -0{\cdot}17$; $P = 0{\cdot}001$, respectively) may have confounded this observation.

Discussion

The results of this population-based study suggest that the basal activity of the renin-angiotensin-aldosterone system, in addition to blood pressure,[2] body mass index,[28] and age,[2] is related to left ventricular mass. In particular, serum aldosterone concentrations in both women and men were found to be associated with septal and posterior wall thickness. In addition, in women there was a strong association between serum aldosterone concentrations and echocardiographic indices of left ventricular mass. Finally, serum ACE activity displayed a strong and independent association with left ventricular mass and hypertrophy, an effect that was, however, restricted to men.

ANGIOTENSIN CONVERTING ENZYME

Growing evidence suggests that serum ACE activity may be higher in subjects with various cardiovascular disorders. In addition to the present finding, myocardial infarction, diabetic nephropathy, and carotid artery thickening have been associated with raised serum ACE concentrations.[18 29–31] Furthermore, in children, serum ACE activity was found to be related to the level of arterial blood pressure.[16]

Serum and tissue ACE activities are largely determined by genetic disposition and vary little in a given individual.[16] Thus it may be hypothesised that genetically determined ACE concentrations may contribute to the genetic risk of developing such cardiovascular disorders.[18 32 33] However, vascular[34 35] or cardiac pressure overload[27] or treatment with ACE inhibitors[36] can also induce ACE gene expression. Therefore, analyses that associate serum ACE activity with cardiovascular disease such as left ventricular hypertrophy cannot be used to establish causal relations.

Interestingly, a deletion polymorphism of the ACE gene that accounts for about 20% of serum[16–18] and tissue[14 37] ACE activities has been related to myocardial infarction, diabetic nephropathy, carotid wall thickness, and left ventricular hypertrophy.[18 30 31] Such molecular genetic association studies, however, fall short of establising a link with a specific gene. Furthermore, a second, at present not yet identified, variant of the ACE gene has been predicted to account for most of the inherited variability of ACE activity.[16 18] Thus at present molecular genetic tools may be of limited sensitivity and specificity in identifying subjects

with inherited high ACE concentrations. Indeed, the ACE deletion polymorphism may not be a strong predictor of the cardiovascular disorders mentioned above. Though numerous reports have supported the original findings,[11 12 38–43] some recent reports were negative.[15 44 45] Nevertheless, the conjunction of both molecular genetic[10–12] and epidemiological methods may overcome some of the limitations of either method and strongly suggest a significant role of ACE in the pathophysiology of left ventricular hypertrophy.

In the present study, in men, an increase of 10 U/l in ACE activity was associated with an estimated increase in left ventricular mass of 8·6 g/m^2. This resembles the estimated increase in left ventricular mass that occurs when systolic blood pressure increases by 20 mm Hg or body mass index increases by 5·2 kg/m^2. Thus given the multifactorial and potentially polygenetic aetiology of left ventricular hypertrophy ACE activity in men accords with other important predictors of this condition.

As in our previous molecular genetic study, we did not see any association between ACE activity and left ventricular mass in women. We cannot explain the mechanism of this apparent gender-related difference. There are, however, analogous situations in ACE "knock-out" mice[46] and genetically hypertensive rats.[47] In particular, in male mice blood pressure seems to be regulated by the level of ACE activity because male transgenic mice that carry only one copy of the ACE gene (and display decreased serum ACE activity) are characterised by significant reduction of systolic blood pressure. In contrast, no changes in blood pressure were detectable in heterozygote female mice missing one copy of the ACE gene.[46] Even more strikingly, Harris *et al* using molecular linkage analysis in male New Zealand hypertensive rats showed that a gene at the ACE gene locus may increase cardiac mass without affecting blood pressure.[47] In female rats, this locus was related to left ventricular mass as well but only in conjunction with higher blood pressure levels. Given the analogies found in human investigations, these experimental models may offer a key to explore the mechanisms that account for the effects of ACE on cardiac growth.

ALDOSTERONE

The present epidemiological observation that serum aldosterone concentrations are associated with cardiac wall thickness accords with numerous lines of experimental and clinical evidence.[48–50] Aldosterone has been shown to have both myocardial and renal effects that substantially affect cardiac metabolism and function. Direct cardiac effects include stimulation of collagen synthesis and fibroblast proliferation. In addition, aldosterone may affect cardiac load indirectly via sodium and volume retention in the distal tubules and the collecting duct of the kidney. With regard to left ventricular hypertrophy, the significance of these cellular mechanisms was suggested by studies in hypertensive patients that found a significant association between serum aldosterone concentrations and left ventricular mass.[49 50] Furthermore, resection of aldosterone secreting adenomas in patients with severe left ventricular hypertrophy was followed by a substantial regression of cardiac hypertrophy.[51] The present data underscore the significance of aldosterone-related cardiac effects, showing that in a population based sample serum aldosterone concentrations correlate with left ventricular wall thickness and in women they also correlate with left ventricular mass.

Serum aldosterone concentration is known to be up-regulated by various mechanisms such as volume depletion, hyperkalaemia, or high concentrations of angiotensin II. Thus the present data cannot be taken to indicate that the observed associations are directly mediated by aldosterone or to establish whether these associations are mediated by myocardial or renal effects. Nonetheless, in both men and women aldosterone concentrations correlated inversely with left ventricular end diastolic diameter. Consequently, concentric remodelling of the left ventricle or concentric left ventricular hypertrophy—that is, geometric patterns that are found in pressure rather than volume overload—were found with raised aldosterone concentrations. These cardiac alterations may be related to an as yet unidentified mechanism that causes cardiac growth, volume contraction, and subsequentially stimulation of aldosterone release. Alternatively, pressure overload and aldosterone could exert additive effects on cardiac growth and remodelling. This notion may be strengthened by the present data which showed that aldosterone effects were most prominent in hypertensive women. Although we cannot define the precise mechanism, given the experimental and clinical data the present study favours the concept that aldosterone is closely related to factors that modulate cardiac geometry and growth.

ANGIOTENSINOGEN

In women serum angiotensinogen has been found to be largely related to oestrogen status,[52] a finding confirmed in the present cohort (data not shown). Most women studied here were postmenopausal and 30% were taking oestrogen replacement therapy. Therefore, this regulatory mechanism may complicate studies like the present that aim to associate slowly progressing structural alterations such as left ventricular hypertrophy with serum angiotensinogen concentrations.

In men serum angiotensinogen concentration, like ACE activity, is partially determined by genetic variants.[53] Some of these variants have been linked to hypertension,[53] an effect that was particularly strong in certain subgroups such as men with normal body mass index.[54] In the present study we found no association between angiotensinogen and left ventricular mass and M mode estimates of left ventricular mass index. However, we found that serum angiotensinogen was related to two dimensional echocardiographic estimates of left ventricular mass index (data not shown).

Subjects in whom both M mode and two dimensional echocardiograms were technically feasible were less obese (body mass index 26·7 *v* 28·6 in M mode group, P = 0·001); this may in part account for the observed discrepancy. Nevertheless, our data fall short of identifying a consistent relation between angiotensinogen and left ventricular mass index and further studies in conjunction with molecular genetic approaches are needed to clarify this issue.

RENIN AND PRO-RENIN

In the present population, no significant positive associations between left ventricular mass and either renin or pro-renin concentrations were detectable. It is noteworthy, however, that in middle-aged subjects renin and pro-renin are regulated by several factors. In particular, renin and pro-renin concentrations have been found to correlate inversely with blood pressure, sodium intake, or angiotensin II, all factors that are known to induce left ventricular hypertrophy.[6 55] Unfortunately, measurements of sodium excretion or angiotensin II are not available in this cohort. Therefore, we cannot exclude the likelihood that renin or pro-renin has independent effects on left ventricular mass, as has been suggested by some but not all previous investigators.[49 50 56]

LIMITATIONS

The statistical regression analyses presented here are based on the means of three measurements of resting blood pressure and a single blood sampling for determination of renin, pro-renin, ACE, angiotensinogen, and aldosterone concentrations. Integration of repeated measurements of either blood pressure (such as 24 hour ambulatory recordings) or circulating components of the renin-angiotensin-aldosterone system may allow better estimation of the haemodynamic load or neurohormonal stimulation that is chronically imposed on the left ventricle.[57–59] Furthermore, we studied the circulating renin-angiotensin-aldosterone system and we cannot estimate the local tissue concentrations of its components. Thus the present study may underestimate the impact of dynamic and local effects of various factors on left ventricular mass. Nevertheless, this epidemiological study may help to extend the substantial experimental evidence on the effects of the renin-angiotensin-aldosterone system on cardiac growth.

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